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Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

PRINCIPAL INVESTIGATOR:

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14. ABSTRACT

The project evaluated fluorine-18 (18F-) fluorocholine positron emission tomography (PET) as an imaging technique for delineating malignancy in the prostate gland. The technique measures tissue metabolism of fluorocholine, a substrate that is preferentially metabolized by cancer cells due to malignant over-expression of the choline transporter and choline kinase enzyme. Based on this measurement, it was proposed that cancerous tissue can be differentiated from benign tissue in the prostate. Project Scope: Men with prostate cancer undergoing radical prostatectomy surgery underwent pre-operative PET scanning to measure fluorocholine uptake in the prostate gland. Imaging results were compared to histopathologic analyses of the prostatectomy specimen to determine the accuracy of prostate cancer sextant localization based on measured fluorocholine uptake. Recruitment of human subjects for this project was completed in 2008. Histologic and immunohistochemical analysis of prostate specimens was performed at the Armed Forces Institute of Pathology. Two subsequent research projects have been derived from the outcome this project. The first project is a research collaboration to develop clinically-oriented image analysis tools for measuring the kinetics of 18F-fluorocholine activity in the prostate gland using PET/CT. The second project is a National Cancer Institute-funded study to conduct clinical trials assessing the treatment response to chemotherapy and anti-androgen therapy using 18F-fluorocholine PET/CT in men with advanced prostate cancer.

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INTRODUCTION

The objective of this project was to develop and evaluate fluorine-18 labeled fluorocholine (18F-fluorocholine) as an imaging agent for positron emission tomography (PET) detection of malignancy in anatomical sextants of the prostate gland. The rationale for evaluating fluorocholine as an oncologic tracer applicable to prostate cancer is based on observations of increased choline and fluorocholine metabolism in malignant prostate tissue relative to normal tissue. Information about tumor activity, location, and volume obtained with PET may have significant clinical value in refining diagnostic and therapeutic approaches against primary prostate cancer.

REPORT SUMMARY

This final addendum report describes the work performed during a no-cost extension period from dates 20 December 2008 to 19 December 2009. Immunohistochemical analysis of prostate tumors using the MIB-1 (Ki-67) immunohistochemical stain was completed at the Armed Forces Institute of Pathology (AFIP) in March 2009. These results were compared to images of the prostate that were obtained pre-operatively using 18F-fluorocholine PET or PET/CT. Appendix 2 contains an abstract summarizing the findings of this radiopathologic correlation study. The completion of this study constitutes the fulfillment of all tasks listed in the project Statement of Work (SOW). Expenditures related to the completion of a radiopathologic correlation study during the current period are summarized below:

Item	Budgeted	Actual
Labor	$12,000	$13,710
Purchased Services (AFIP)	$25,000	$25,190
Travel	$1,200	-
Admin Supplies	$700	-
Indirect Costs (67%)	$26,063	$26,063
TOTAL	**$64,983**	**$64,963**

Table: Expenses for the current no-cost extension period

BODY

Prostate cancer remains the second leading cause of male cancer death in the United States. If treated at an organ-confined stage, the expected 5-year survival from prostate cancer is 100% as compared to a 33% 5-year survival for metastatic prostate cancer *(1)*. In vivo imaging capable of localizing prostate cancer may increase the rate of early detection and improve pre-treatment risk stratification and treatment decision-making. The goal of this study was to evaluate the potential diagnostic and prognostic value of 18F-fluorocholine PET and PET/CT imaging as a method for imaging primary prostate cancer.

Items Relevant to SOW Task 1: Study Preparation

This task was completed as described in the previous year's Addendum Report.

Items Relevant to SOW Tasks 2: Subject Recruitment and Data Collection

This project was an IRB-approved clinical research study that enrolled 25 human subjects. Subject recruitment has been completed in the previous year and the study has been officially closed to further accrual since 9 June 2008. A human subjects study completion letter was submitted to the Human Research Protection Office (HRPO) on 7 October 2009. Records indicate there were no adverse events, unanticipated problems involving risks to subjects or others, withdrawal of subjects from research, or complaints about the research during the lifetime of the project.

Task 2d was completed in March 2009. Task 2d consisted of immunohistochemical analysis of prostate specimens for expression of the Ki-67 antigen. This work was completed under the

supervision of Dr. Isabell Sesterhenn (Chief, Genitourinary Pathology at AFIP). While at Walter Reed Army Medical Center (WRAMC), Dr. Kwee also met with Dr. David McLeod (Director, Center for Prostate Disease Research) and members of the Urology Department at WRAMC to discuss potential translational and clinical applications of the study results. Completion of Task 2d constituted the completion of the remainder of Task 2.

Ki-67 analysis has previously been shown to have potential prognostic value as a marker of tumor proliferation in clinically localized prostate cancer (7). A hypothesized correlation between tumor 18F-choline uptake and expression of Ki-67 would lend support for the potential prognostic value of 18F-fluorocholine PET/CT as a prostate imaging modality. Appendix 2 contains a scientific abstract which summarizes the results of the radiohistopathologic correlation study comparing the immunohistochemical findings with 18F-fluorocholine PET/CT. Data from 24 of the 25 subjects was available for this correlation study due to a computer malfunction at TAMC that resulted in the loss of PET/CT data from one subject. Although higher 18F-choline uptake was an indicator of malignant prostate tumors (as we previously reported), no statistically significant correlation between prostate tumor Ki-67 labeling and prostatic 18F-fluorocholine uptake was observed. This finding supports the possibility that tumor uptake on 18F-fluorocholine PET/CT may be reflective of other characteristics of malignancy besides proliferative activity. The abstract will be submitted for presentation at a scientific meeting in 2010 (conference TBD).

Items Relevant to SOW Task 3: Data Analyses

The completion of this task was described in the previous year's Addendum Report.

Items Relevant SOW Task 4: Reporting and Design of Secondary Studies

A grant proposal to investigate 18F-fluorocholine PET/CT for monitoring therapeutic response to chemotherapy and hormone therapy in advanced metastatic prostate cancer received funding from the National Cancer Institute in June 2009 (NIH R21CA139687, PI- Kwee). Imaging protocols developed during the current study are being used in the two clinical imaging trials supported by this grant. These trials are evaluating 18F-fluorocholine PET/CT for whole-body monitoring of therapeutic response in advanced prostate cancer. Appendix 3 contains summaries of these clinical studies along with a peer-reviewed publication that summarizes the pilot data for this project and its imaging protocols.

In addition, a collaborative study between The Queen's Medical Center and Phillips Research (Phillips Medical Systems, N.A.) has been initiated to study prostatic 18F-fluorocholine kinetic analysis as a potential means to further improve the sextant localization of primary prostate cancer. The rationale for this study is based on observations of rapid kinetic uptake of 18F-fluorocholine by the prostate tumors observed in the current study. This parametric analysis of 18F-fluorocholine PET/CT data was summarized in the previous year's Addendum Report (Appendix 2, Reference 5, from 2008 Addendum Report).

KEY RESEARCH ACCOMPLISHMENTS DURING THE CURRENT PROJECT PERIOD

- A radiopathologic correlation study between 18F-fluorocholine PET/CT of the prostate and Ki-67 immunohistochemical analysis of the whole prostate specimen was completed in the current period.

- A grant proposal to evaluate 18F-fluorocholine PET/CT for monitoring and predicting treatment response in androgen-insensitive and hormone-refractory prostate cancer has received funding from the National Cancer Institute. This new project employs 18F-fluorocholine PET/CT imaging protocols first used and tested by the current project.

NOTE: Research accomplishments from previous years are not included in this report.

REPORTABLE OUTCOMES

This Final Addendum Report lists all reportable outcomes since 2006. Publication reprints from previous years are available in previous reports.

Subsequent Federal Research Project Funding:

Treatment Effects on Tumor 18F-Choline Metabolism in Advanced Prostate Cancer
National Institutes of Health, National Cancer Institute
R21CA139687 Dates: 7/2009 – 6/2011 Total Federal Award Amount: $766,480
Principal Investigator: Sandi Alexander Kwee, MD

Other Subsequent Research Projects:

Dynamic PET Study of Prostate Cancer with 18F-Fluorocholine.
Philips Research NA.
Performance Dates: March 1 2007 to June 30 2010
Principal Investigator: Sandi Alexander Kwee, MD

Peer-Reviewed Journal Publications:

Kwee SA, DeGrado TR, Talbot JN, Gutman F, Coel MN. Cancer Imaging with Fluorine-18 Labeled Choline Derivatives. Seminars in Nuclear Medicine. 37: 420-428. November 2007.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Use of Step-Section Histopathology to Evaluate 18F-Fluorocholine PET Sextant Localization of Prostate Cancer. Molecular Imaging 2008. Jan-Feb;7(1): 12-20.

Kwee SA, Coel MN, Ly BH.18F-choline PET/CT Imaging of RECIST Measurable Lesions in Androgen Insensitive Prostate Cancer. Annals of Nuclear Medicine. 2009 Aug; 23(6): 541-548

Abstracts (Oral Presentations):

G. Thibault, R. Stack, **S. A. Kwee**, B. Furusato, M. Coel and I. Sesterhenn. *Initial Results From a Whole Prostate Histopathologic Correlation Study.*, American Urologic Association – Western Section. Annual Meeting. October 2006.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Non-Invasive Detection and Therapeutic Targeting of Cancer in the Prostate Using Fluorine-18 Fluorocholine Positron Emission Tomography. IMPact 2007, Atlanta, GA.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Prostate Imaging with 18F-Fluorocholine Using a Whole-Body Positron Emission Tomograph. Nuclear Science Symposium / Medical Imaging Conference Institute of Electrical and Electronics Engineers 2007.

Stack R, Thibault R, **Kwee S**, Furusato B, Potter K, Coel MN, Sesterhenn I. *Comparisons Between Prostate Histopathology and Imaging with 18F-Fluorocholine PET.* The 54th Annual Kimbrough Urological Seminar. January 2007.

Park H, **Kwee S**, Thibault G, Stack G, Furusato B, Sesterhenn I, Meyer CR. Registration Methods for Histological Slides and *ex vivo* MRI of Prostate. Nuclear Science Symposium / Medical Imaging Conference Institute of Electrical and Electronics Engineers 2007.

Kwee SA, Ly B, Coel MN. RECIST measurability of 18F-fluorocholine PET/CT detected lesions in androgen insensitive prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Narayanan M, **Kwee SA,** Coel MN, Lim J. Kinetic analysis of 18F-fluorocholine PET/CT images for sextant localization of primary prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Abstracts (Published):

Kohli V, **Kwee SA**, Coel MN. *Comparison between 2D and 3D Prostate PET Imaging.* J. Nucl. Med., May 2006; 47: 370P.

Kwee SA, Turner H, Lim J, Wakano C, Coel M. *Dimethylaminoethanol Reduces 18F-Fluoroethylcholine Uptake in Prostate Cancer Cells.* J. Nucl. Med., May 2006; 47: 425P.

Kwee S, Wei H, Sesterhenn IA, Yun DY, Coel MN. *Intensity Modulated Radiation Therapy For Prostate Cancer With Radiation Dose Augmentation Guided By 18F-FCH PET Imaging.* J. Nucl. Med., May 2006; 47: 457P.

Kwee SA, Thibault G, Stack R, Furusato B, Coel M, Sesterhenn IA. *Cancer Localization in the Prostate with 18F-Fluorocholine PET: Initial Results From a Whole Prostate Histopathologic Correlation Study.* J. Nucl. Med., May 2006; 47: 459P.

Lim J, **Kwee S**, Cabral C, Turner H, Wakano C, Stokes A, Coel M. *Automated Synthesis and In Vitro Uptake of [18F] Fluoroethylcholine in Prostate Cancer*. Molecular Imaging Jul-Sep 2006 5(3).

Kwee SA, Coel MN, Lim J. Longitudinal 18F-fluorocholine PET/CT imaging in prostate cancer patients with increased risk of disease progression. 56th Annual Meeting of the Society of Nuclear Medicine. June 13-17, 2009.

Letters To The Editor

DeGrado T, **Kwee SA,** Coel MN, Coleman RE. The Impact of Urinary Excretion of ^{18}F-Labeled Choline Analogs J Nucl Med 2007 48: 1225 (letter)

Kwee SA, Degrado T. Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels. Eur J Nucl Med Mol Imaging. 2008 Aug; 35(8): 1567-9 (letter).

Kwee SA, Degrado T. Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels. Eur J Nucl Med Mol Imaging. 2008 Aug; 35(8): 1567-9.

Personnel Supported by the Research Project

Sandi A. Kwee, MD	Principal Investigator
Marc N. Coel, MD	Co-Investigator
Isabel Sesterhenn, MD	Limited to Payment for Services Rendered through AFIP
Richard Stack, MD	Limited to DoD Approved Reimbursement for Travel Expenses
Gregory Thibault, MD	Limited to DoD Approved Reimbursement for Travel Expenses

CONCLUSION

This is the final Addendum Report for Project W81XWH-05-1-0056. All project tasks as described in the Statement of Work have been successfully completed. The task of immunohistochemical analysis of the prostate specimens was completed during this period. Products from this research project have led to the initiation of two National Cancer Institute funded clinical trials (Trial ID NCT00928252 and NCT00928174 on clinicaltrials.gov) to assess 18F-fluorocholine PET/CT as a marker of clinical outcome, pain, and quality of life in advanced prostate cancer.

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APPENDIX 1: Statement of Work (Revised July 2006)

Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

Task 1. Study Preparation, Months 1-4:

a. Finalize research protocol and study-specific forms.

b. Obtain institutional review board (IRB) approval of study protocol and consent form at project sites: Tripler Army Medical Center (TAMC), Queen's Medical Center (QMC), and the Armed Forces Institute of Pathology (AFIP).

c. Orient all study personnel on protocol and methods.

Task 2. Subject Recruitment and Data Collection, Months 4-20:

a. Begin subject recruitment at TAMC and QMC. A total of 25 subjects will be recruited from both sites over a 16 month period.

b. Subjects will undergo whole-body F-18 FCH PET or PET/CT scanning to acquire images of the prostate gland.

c. Subjects not undergoing PET/CT will undergo a separate CT at QMC.

d. Following surgery, the prostatectomy specimens will delivered to AFIP for processing and analysis. Analysis procedures include surgical histopathology and immunohistochemical staining for the Ki-67 antigen. The data will be recorded on study-specific pathology forms.

e. All data will be entered into a study database for analysis.

Task 3. Data Analyses, Months 6 – 20:

a. PET or PET/CT image analysis will be performed by two physicians.

b. Collected data will be analyzed and correlated in periodic interim analyses. Interim results will be summarized in annual reports.

Task 4. Final Analyses/Reporting and Design of Secondary Studies, Months 20-24:

a. Finalize analysis of data and summarize results as stated in the specific aims.

b. Prepare final report and manuscripts for publication.

c. Design secondary studies using the collected data.

APPENDIX 2:

Abstract

Tumor 18F-choline Uptake May Not Reflect Proliferative Activity in Primary Prostate Cancer.

Kwee SA, Thibault G, Stack R, Furusato B, Coel MN, Sesterhenn IA.

Purpose: Immunohistochemical Ki-67 labeling (MIB-1 index) has been shown to have potential prognostic value in clinically localized prostate cancer. To determine whether 18F-choline PET/CT can provide a prognostic measure of tumor proliferation in primary prostate cancer, we compared the immunohistochemical MIB-1 labeling index to tumor 18F-choline uptake corresponding to malignantly involved prostate sextants as determined through step-section analysis of the prostate following radical prostatectomy. Materials and Methods: Histopathologic analysis was performed on completely embedded whole-mounted prostate specimens from 24 subjects who received pre-operative prostate 18F-choline PET or PET/CT imaging. The PET images were acquired 10 minutes following intravenous administration of 3.3 to 4 MBq/kg of 18F-choline. The images were analyzed by region of interest analysis to obtain the maximum standardized uptake value (SUVmax) corresponding to prostate sextants. Diagnostic accuracy was estimated by receiver operator characteristic (ROC) analysis. Discrete tumors measuring at least 5mm in diameter were identified for assessment of the MIB-1 labeling index. The evaluation for Ki-67 antigen expression was performed by antigen retrieval and immunohistochemical labeling with the monoclonal antibody MIB-1. A labeling index for each malignantly involved sextant was expressed as the percentage of tumor cells demonstrating nuclear staining in each section. Regression analysis was performed to assess the correlation between immunohistochemical labeling index and SUVmax in the most active prostate sextant for each tumor. Results: The average weight of the prostate specimens was 46 grams (s.d. 23 grams). The average total tumor volume was 8.2 cc (s.d. 9 cc). Two patients who received hormonal therapy acutely prior to surgery were excluded from ROC analysis since the PET/CT images from both patients demonstrated globally diminished prostatic activity. Treatment effects were also evident on histopathologic analysis of the prostate specimens from these patients. The computed area under the ROC curve (AUC) was 0.80 (sensitivity 82% if specificity 60%). Thirty-four macroscopic and discrete tumors (1 to 3 per specimen) were available for Ki-67 analysis. The correlation between MIB-1 labeling index and sextant SUVmax in malignant sextants was not statistically significant ($r=0.12$, $p=0.5$). No significant correlation between Gleason sum score and SUVmax was observed. Discussion: Acute administration of hormonal therapy may result in diminished prostatic 18F-choline uptake on PET/CT. This observation suggests that 18F-fluorocholine PET/CT may have value as a means of measuring therapeutic response in prostate cancer. The lack of a significant correlation between tumor Ki-67 expression and 18F-fluorocholine uptake in primary prostate cancer suggests that 18F-fluorocholine uptake may not strongly reflect tumor cell proliferation in the prostate gland. Increased 18F-fluorocholine uptake by malignant prostate tumors may relate to a characteristic other than increased proliferative activity in malignancy.

APPENDIX 3:

Reprints and Descriptions of Subsequent Studies

(Descriptions were downloaded from the Clinicaltrials.gov website)

Ann Nucl Med (2009) 23:541–548
DOI 10.1007/s12149-009-0273-1

ORIGINAL ARTICLE

^{18}F-choline PET/CT imaging of RECIST measurable lesions in hormone refractory prostate cancer

Sandi A. Kwee · Marc N. Coel · Bevan H. Ly · John Lim

Received: 2 March 2009 / Accepted: 2 May 2009 / Published online: 16 June 2009

Abstract
Purpose Apply measurability criteria based on the response evaluation criteria in solid tumors (RECIST) to lesions found on ^{18}F-choline positron emission tomography (PET)/computerized tomography (CT) in patients with hormone refractory prostate cancer.
Methods Whole-body PET followed by CT or in-line PET/CT using 3.3–4 MBq/kg of ^{18}F-choline was performed prospectively on 30 patients with prostate cancer, castrate testosterone levels, and rising post-treatment prostate specific antigen (PSA) levels. Lesions demonstrating increased ^{18}F-choline uptake were classified as measurable or non-measureable based on RECIST.
Results Three patients were known previously to have RECIST measurable lesions, 10 patients had metastatic findings on radionuclide bone scan, and 17 patients had elevated serum PSA level as the only evidence of disease. Lesions demonstrating increased ^{18}F-choline uptake were found in 28 (93%) patients. Thirty-eight PET/CT lesions from 14 patients were measurable by RECIST. Lymph node maximum standardized uptake value (SUV_{max}) correlated with lymph node diameter (Pearson $r = 0.44$, $p < 0.001$). RECIST measurable lymph node SUV_{max} was significantly higher than that of non-measurable nodes (8.1 vs. 3.7, $p < 0.0001$). Detection of skeletal, prostatic, or RECIST-compatible lesions was more likely with a PSA level greater than 4.0 ng/ml (Fisher exact $p = 0.0005$).
Conclusion Lesions detected with ^{18}F-choline PET/CT are frequently measurable by RECIST at baseline. Therefore, it may be feasible to include comparisons to RECIST in evaluations of ^{18}F-choline as a therapeutic response marker for hormone refractory prostate cancer.

Keywords Positron emission tomography · Fluorocholine · Prostate carcinoma

Introduction

Chemotherapy has traditionally been considered ineffective at prolonging the survival of patients with hormone refractory prostate cancer (HRPC). However, two large clinical trials (TAX 327 and Southwest Oncology Group 99-16) recently demonstrated improved survival in patients with progressive HRPC treated with docetaxel-based chemotherapy [1, 2]. Although these studies rekindled a role for chemotherapy in progressive HRPC, the survival benefits reported in these studies were modest, on the order of 2–3 months. Therefore, there is continuing interest in new chemotherapeutic agents or agents which can be combined with docetaxel to further enhance survival in HRPC.

Unfortunately, the task of quantifying disease progression in patients with HRPC is difficult and continues to hinder the progress of clinical trials [3, 4]. Morphologic criteria such as the response evaluation criteria in solid tumors (RECIST), used in cancer trials to measure tumor response, have proven difficult to apply to prostate cancer

The findings and conclusions expressed in this study do not necessarily represent the views of The Queen's Medical Center.

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[3, 5]. Not only is the prostate excluded as a measurable disease site by RECIST, but also the skeletal system which often dictates morbidity and mortality in HRPC is also largely ignored by these criteria. While soft-tissue metastases are considered measurable by standard imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), such lesions may be difficult to find in many patients with advanced prostate cancer. In one study, conventional radiographic workup yielded RECIST measurable lesions in only 43 and 16% of patients with castrate and non-castrate metastatic prostate cancer [3]. Consequently, many patients with HRPC could be excluded from clinical trials if RECIST were used exclusively to define study endpoints or eligibility.

Choline is essential for the synthesis of cell membrane phospholipids. Observations of upregulated choline metabolism and increased choline kinase expression in cancer have fueled interest in radiolabeled choline derivatives as oncologic tracers for positron emission tomography (PET) [6, 7]. This approach has shown feasibility in prostate cancer using the tracer fluorine-18 fluoromethylcholine (^{18}F-choline) [8–11]. As a preliminary step in evaluating ^{18}F-choline PET/CT as a method for measuring prostate cancer tumor response, we assessed the frequency of RECIST compatible lesions identified on ^{18}F-choline PET/CT in patients with HRPC.

Method

Subjects

The study was approved by our institutional review board. All patients provided written informed consent. Thirty consecutive patients were enrolled prospectively. The criteria for enrollment was a diagnosis of HRPC based on a rising serum prostate specific antigen (PSA) level with castrate levels of testosterone while on anti-androgen therapy. Furthermore, the rise in PSA was documented on three occasions more than 1 week apart, with a total rise of more than 50% from baseline at enrollment.

Synthesis of ^{18}F-choline

Synthesis was performed using a chemical process control unit (CTI/Siemens CPCU, CTI/Siemens, Knoxville, TN) [12]. Tracer was synthesized by fluorination of ditosylmethane with fluorine-18 followed by alkylation of the fluorotosylmethane intermediate with dimethylethanolamine. Product was trapped onto a silica Sep-Pak (Waters Corporation, Milford, MA) while dimethylethanolamine, a competitive inhibitor of choline kinase, was removed by washing with ethanol and water. Final product was eluted with 2% acetic acid, neutralized, and made isotonic for injection. Radiochemical purity was assayed by high performance liquid chromatography (^{18}F-choline eluted at 6.8 min) and thin layer chromatography. Radiochemical purity was >99%.

PET imaging

PET was performed on patients 1–12 using a Hamamatsu SHR-22000 PET scanning instrument (Hamamatsu Photonics, Hamamatsu-City, Japan) with spatial resolution near the field of view center of 3.5 mm transaxially and 4.2 mm axially. Transmission scans of the body in the supine position were acquired using two Germanium-68 rod sources over 4 or 5 fields of view starting from the pelvis. Transmission scans at each field lasted 3 min. Ten minutes after intravenous injection of 3.3–4 MBq/kg of ^{18}F-choline, corresponding emission scans in 2D-mode were acquired at 7 min per field of view. Image reconstruction employed an ordered subsets expectation maximization algorithm. Segmented attenuation correction was based on the measured transmission data. A subsequent non-contrast CT of the abdomen or pelvis was performed within 7 days if abnormal ^{18}F-choline uptake was noted on PET. CT was performed using a 4-channel multi-detector CT scanner (Picker MX 8000; Marconi Medical Systems, Cleveland, OH) with the following parameters: 120 kV, 200 mA/slice, rotation time 0.5 s, slice thickness/interval 3.0 mm.

PET/CT was performed on patients 13–30 using a Philips Gemini TF-64 PET/CT scanner (Philips Medical Systems, N.A., Bothell, WA) with spatial resolution near the field of view center of 4.8 mm in transverse and axial directions [13]. A CT transmission scan in the supine position was acquired from the pelvis to the skull. The 64-channel helical CT scanning parameters were: 120 kVp, 50 mA/slice, rotation time 0.75 s, slice thickness/interval 5.0 mm. No intravenous contrast was used with CT. At 10 min after intravenous injection of 3.3–4 MBq/kg of ^{18}F-choline, emission scans were acquired from mid-thigh to skull over 8–11 bed positions at 2 min per position. Image reconstruction employed a list-mode version of a maximum likelihood expectation maximization algorithm with a time-of-flight kernel applied in both the forward- and back-projection operations. CT data were used for attenuation correction.

Image analysis

Visual image analysis was performed by two readers with blinding to clinical data at the time of interpretation (S.K., M.C.). PET images were assessed visually for areas of increased ^{18}F-choline uptake as determined by reader

consensus. Both readers have experience in interpreting ^{18}F-choline uptake in primary and metastatic prostate cancer [14, 15]. Images acquired from 10 healthy male control subjects using the Gemini TF-64 PET/CT and images acquired from 10 men with primary brain tumors and no other known malignancies using the Hamamatsu SHR-22000 were used as references for normal ^{18}F-choline biodistribution. None of these reference scans demonstrated extracranial uptake that could be classified as a lesion by the study criteria.

PET and CT images were spatially registered and reviewed on a workstation (Hermes, Hermes Medical Solutions, Battle Ground, WA). PET and CT could be viewed separately or alpha-blended in a single image. Region of interest (ROI) analyses and morphometry were performed on separate PET and CT windows. Lesions demonstrating increased ^{18}F-choline uptake were anatomically categorized as a skeletal lesion, prostate lesion, or tissue lesion. Increased uptake was defined as visually discernable activity above normal tissue activity or background activity in the case of lymph nodes. For this study, inguinal lymph nodes were not classified because benign inguinal nodes can transiently demonstrate increased ^{18}F-choline uptake [10].

The maximum standardized uptake value (SUV_{max}) of each lesion was measured by ROI analysis. Standardized uptake value is defined as measured voxel activity divided by injected radioactivity normalized to body weight. Because ^{18}F-choline is not re-absorbed by the kidneys (Fig. 1), focal activity along the ureteral tract was not considered to be a potential lesion to avoid the possibility of misclassifying excreted activity as a lesion.

Lesions exhibiting increased ^{18}F-choline uptake were classified as measureable or non-measureable based on published guidelines on RECIST [5]. As recommended by RECIST, prostate and skeletal lesions were deemed non-measureable. The longest diameter of all tissue lesions was measured on the CT images. Because helical CT was used, a diameter of 10 mm or greater defined a measurable lesion. Lymph nodes clusters were considered a single lesion if their delineation could not be made on the basis of CT.

Radionuclide bone scan findings were compared with the skeletal findings on PET/CT. Bone scans performed within the past 12 weeks were classified according to their clinical reports as positive or negative for skeletal metastases. In patients with positive bone scans, results were further classified as demonstrating "new lesions" or "no new lesions" based on Prostate Cancer Working Group 2 recommendations for bone scan interpretation [16].

Statistical analysis

Differences in sample means were tested for significance using Student's t test. Dichotomous associations were assessed by Fisher's exact test using two-sided p values. Correlation was measured using the Pearson product moment coefficient. A p value of less than 0.05 was considered significant. Statistical analysis was performed using SAS Version 9 (SAS Institute Inc., Cary, NC). Because imaging studies were not compared to histopathologic reference data, sensitivity and specificity were not estimated.

Results

The mean age was 70 years (range 58–86 years). The mean and median PSA level was 175 and 12 ng/ml at enrollment (range 0.9–3383 ng/ml). Three patients were known to have RECIST measurable lesions (Table 1: patients 11, 18, and 25), 9 patients had new metastatic findings on radionuclide bone scan, 1 patient had previous metastatic findings on bone scan that were decreasing in intensity on the most recent scan, and 17 patients had elevated serum PSA level as the only evidence of disease. Lesions demonstrating increased ^{18}F-choline uptake were identified in 28 (93%) out of 30 patients. All 24 patients with PSA levels of

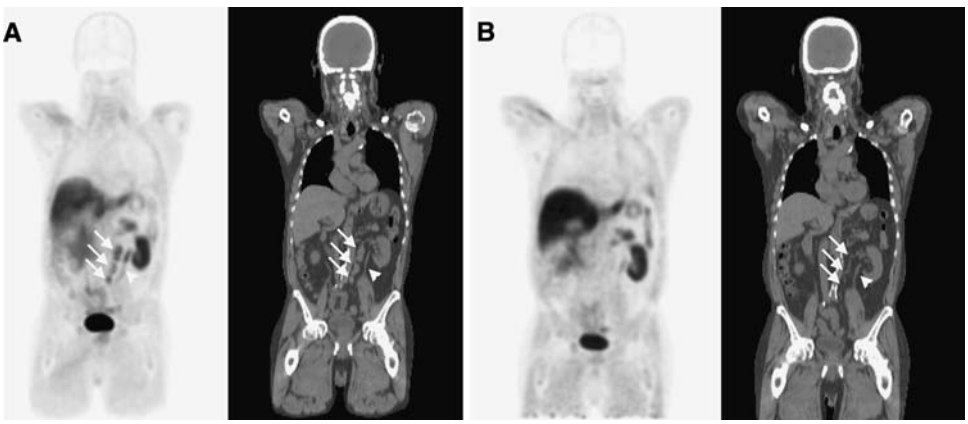

Fig. 1 RECIST measurable lesions responding to chemotherapy. **a** PET (*left*) and CT (*right*) shows increased ^{18}F-choline uptake in 3 para-aortic lymph nodes (*arrows*) measuring 22, 16, and 18 mm in diameter. Adjacent ureter shows normal excretion of ^{18}F-choline (*arrowhead*). **b** PET (*left*) and CT (*right*) repeated after four cycles of docetaxel chemotherapy shows loss of ^{18}F-choline uptake and reduced lymph node size (*arrows*)

Table 1 Patient characteristics

ID	Age	PSA (ng/ml)	Gleason score	Primary treatment history	New lesions on bone scan (#days before PET)	Prostate lesion on PET (SUV_{max})	Skeletal lesions on PET (SUV_{max})	#Tissue lesions ≥10 mm (highest SUV_{max})	#Tissue lesions < 10 mm (highest SUV_{max})
1	78	11.9	4 + 5	RT	No (7)	Yes (4.2)	No	0	0
2	68	9.3	4 + 5	RT	No (23)	Yes (7.4)	No	0	2 (5.1)
3	67	12	3 + 4	RT	No (1)	Yes (5.3)	No	0	0
4	69	113	4 + 4	RT	Yes (21)	No	Yes (11.1)	0	0
5	65	214	4 + 5	RT	Yes (21)	Yes (4.4)	Yes (8.2)	0	0
6	74	14.7	4 + 5	RT	Yes (19)	No	Yes (9.1)	1 (15.1)	0
7	79	140	4 + 3	RP	Yes (19)	No	Yes (4.4)	0	0
8	68	11.6	3 + 4	RP	–	No	No	4 (11.7)	0
9	79	200	4 + 5	RT	No (20)	No	Yes (9.4)	0	0
10	84	210	4 + 5	RT	Yes (24)	Yes (6.6)	Yes (7.2)	2 (4.2)	0
11	66	222	4 + 5	RT	No (8)	Yes (9.3)	No	16 (14.7)	5 (7.6)
12	57	12	4 + 5	RT	No (30)	No	No	1 (9.9)	0
13	75	3383	4 + 5	RT	Yes (6)	No	Yes (9.0)	0	0
14	58	1.9	4 + 4	RP, RT	–	No	No	1 (3.7)	0
15	76	2.4	3 + 4	RT	Yes (2)	No	Yes (2.4)	0	1 (2.0)
16	63	6.6	4 + 4	RP	–	No	No	1 (3.5)	1 (2.4)
17	60	26.6	4 + 4	RP	–	No	No	1 (5.0)	2 (3.0)
18	74	197	4 + 4	RT	No (28)	Yes (7.1)	No	4 (5.6)	0
19	68	146	4 + 3	RT, orchiectomy	–	No	No	1(4.3)	3 (3.5)
20	74	3	4 + 3	RT	No (20)	No	No	0	1 (2.7)
21	62	4.3	4 + 5	RT	No (21)	No	No	2 (2.9)	1 (1.4)
22	62	253	4 + 3	RT	Yes (21)	No	Yes (6.3)	0	0
23	68	3.4	4 + 4	RP	No (25)	No	No	0	0
24	76	9	4 + 3	RT	–	Yes (15.0)	No	0	0
25	58	20	4 + 5	RT, chemotherapy	No (30)	Yes (2.3)	No	1 adrenal mass (11.0)	0
26	58	4.6	3 + 4	RP, RT	No (21)	No	No	1 (5.9)	0
27	65	11	3 + 4	RT	No (41)	No	No	2 (4.0)	0
28	86	0.9	3 + 4	RP	No (6)	No	No	0	1 (2.7)
29	80	1.27	4 + 5	RT	No (72)	No	No	0	0
30	80	12.7	4 + 5	RT	Yes (14)	Yes (2.6)	Yes (3.9)	0	0

PSA prostate specific antigen, *RP* radical prostatectomy, *RT* radiation therapy, SUV_{max} maximum standardized uptake value

greater than 4.0 ng/ml demonstrated increased ^{18}F-choline uptake in either the skeletal system, the prostate gland, or a RECIST compatible lesion. Twelve of these patients had at least one measurable lymph node on PET/CT. The association between PSA greater than 4.0 ng/ml and increased ^{18}F-choline uptake in a skeletal, prostatic, or RECIST-compatible lesion was significant (Fisher exact $p = 0.0005$). Increased ^{18}F-choline uptake limited to non-measurable lesions of the skeleton, prostate, or a combination of non-measurable lesions were noted in 5, 4, and 3 patients, respectively. Of 6 patients with a PSA level of less than 4.0 ng/ml, 2 exhibited no areas of increased ^{18}F-choline uptake, 3 showed uptake limited to non-measurable lesions, and 1 showed increased ^{18}F-choline uptake corresponding to a measurable lesion (a single 10 mm lymph node).

Tissue lesions

Focal uptake in the prostate gland was observed in 10 (33%) out of 30 patients. Four of these patients had RECIST measurable lesions in other areas. A total of 55 non-prostate tissue lesions were identified in 18 (60%) patients on the basis of increased ^{18}F-choline uptake (example shown in Fig. 1). These extraprostatic lesions corresponded to 54 lymph nodes and 1 adrenal mass, all also evident on CT alone. Of these, 38 (69%) lesions from 14 (47%)

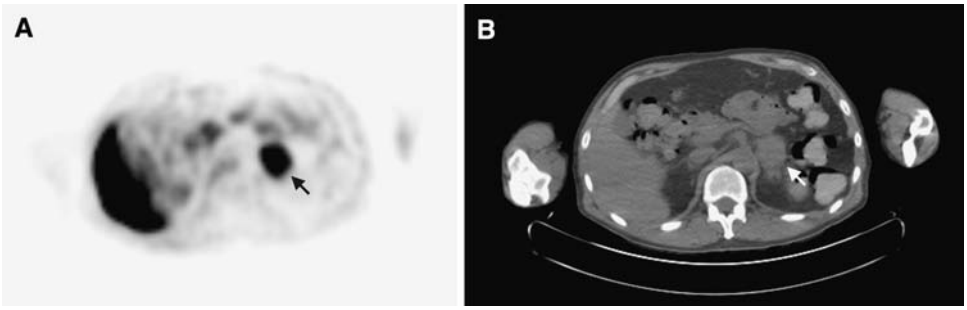

Fig. 2 ^{18}F-choline uptake by an adrenal metastasis. **a** PET demonstrates increased tracer uptake in the left adrenal gland with a maximum SUV of 11.0. **b** Corresponding CT image shows an enlarged left adrenal gland with maximum transverse diameter of 32 mm. This biopsy-confirmed metastasis is measurable on the basis of RECIST and therefore may serve as a target lesion that can be monitored over the course of chemotherapy

patients measured 10 mm or greater in diameter and were classified as measureable lesions, including the adrenal mass which was confirmed by biopsy to be a metastasis (Fig. 2).

The mean SUV_{max} of RECIST measurable lymph nodes was significantly greater than in RECIST non-measurable lymph nodes (8.1 vs. 3.7, $p < 0.0001$). Because the results could be skewed by a disproportionate number of lymph nodes in one patient, differences in SUV_{max} were also tested for significance excluding the data from patient 11. Following this exclusion, the mean SUV_{max} of RECIST measurable lymph nodes remained significantly greater than that of RECIST non-measurable lymph nodes (5.8 vs. 2.9, $p < 0.001$). The correlation between lymph node diameter and lymph node SUV_{max} was statistically significant (Pearson $r = 0.44$, $p < 0.05$ including patient 11; Pearson $r = 0.51$, $p < 0.05$ excluding patient 11; Fig. 3).

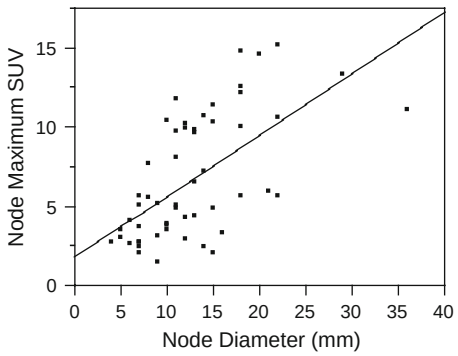

Fig. 3 Graph showing the relationship of lymph node maximum diameter (mm) to lymph node maximum standardized uptake value (SUV)

Skeletal lesions

Bone scans performed within 3 months of the study were available from 24 patients. The mean time interval between bone scan and PET was 18 days (range 1–72 days). In 14 (58%) of these patients, bone scans showed no evidence of skeletal metastasis. In 13 of the 14 patients, PET demonstrated no focal increases in skeletal activity. In one patient (subject 9), increased lumbar vertebral activity was noted on ^{18}F-choline PET although the corresponding bone scan was negative. Clinical and radiographic evidence of skeletal metastatic progression, particularly in the lumbar spine, appeared within 12 months indicating a true-positive finding on the original PET scan (Fig. 4).

In 9 patients, new lesions were identified on the most recent bone scan as compared to a previous scan. PET demonstrated foci of increased skeletal uptake in all 9 patients. In one patient (subject 21), the most recent bone scan was positive for skeletal metastases, but showed fewer lesions than the previous scan, suggesting treatment-related regression of skeletal metastases. No increases in skeletal ^{18}F-choline uptake were observed in this patient.

Discussion

A consensus committee of clinical investigators recently adopted a clinical states model of prostate cancer to facilitate trial design and patient management [16]. This model provides a working framework for measuring and reporting outcomes based on disease manifestation, taking into account well-known problems in disease assessment under certain clinical situations. The committee revised criteria for authenticating disease progression using existing imaging techniques without precluding the future adoption of advanced imaging techniques such as PET/CT or MRI. The criteria incorporate RECIST, although additional criteria were included partly to overcome the limitations of RECIST in prostate cancer. Because the evaluation of molecular imaging in clinical trials would benefit from comparisons against conventional methods, we sought to determine the feasibility of evaluating tumor responses to chemotherapy with ^{18}F-choline PET/CT by

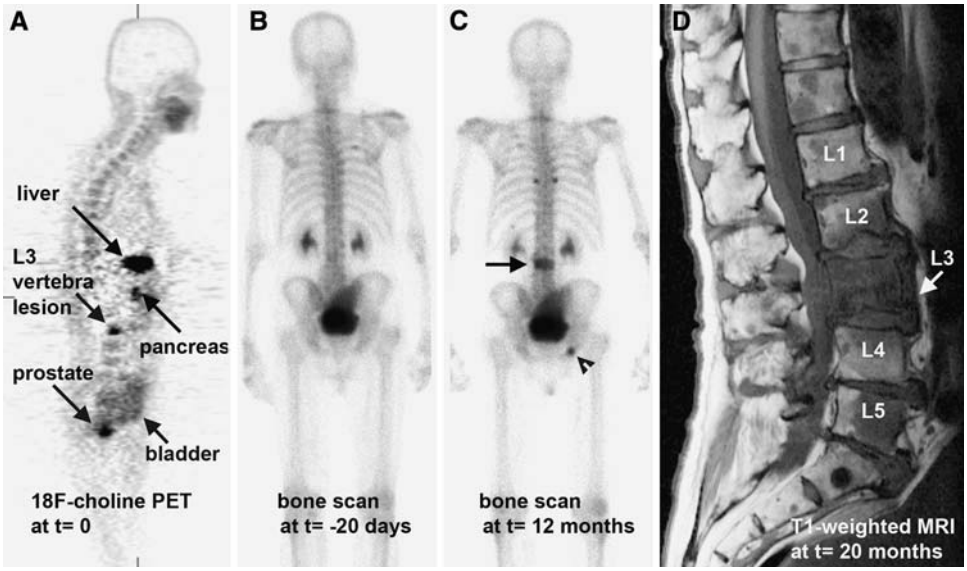

Fig. 4 Early detection of bony metastases by ^{18}F-choline PET. **a** PET demonstrates increased uptake in the lumbar spine (L3 is shown) and prostate gland. **b** Bone scan performed 20 days earlier demonstrated no metastases. **c** Twelve months later, bone scan demonstrates new L3 vertebral (*arrow*) and right ischial (*arrowhead*) abnormalities. **d** MRI at 20 months confirmed vertebral metastatic involvement that was most extensive at L3

applying the original RECIST criteria at baseline to PET/CT detected lesions in patients with HRPC.

Tissue lesions measurable by RECIST were found in 47% of study patients. This percentage of patients with measurable disease is not significantly higher than reported in other studies, possibly because lymph node pre-dominant disease is less common than skeletal metastatic disease [3]. Taking skeletal and prostate lesions into account, abnormal findings were identified in 93% of the patients in this study. This could imply that a significant amount of disease may be overlooked by prostate cancer clinical trials that rely heavily on RECIST as a surrogate marker of response.

There are a number of studies that have preliminarily evaluated ^{18}F-choline PET/CT for clinical staging of prostate cancer. In high-risk patients with clinically localized prostate cancer (pre-prostatectomy, PSA $>$ 10 ng/ml, Gleason sum $>$ 7, non-castrate), Hacker et al. [17] reported that ^{18}F-choline PET/CT was less sensitive than extended pelvic lymph node dissection or sentinel pelvic lymph node dissection for detecting pelvic lymph node metastases. This is not surprising given that most lesions would likely fall below the spatial resolution of PET/CT at this early stage [18]. At more advanced stages of disease, Price et al. [10] demonstrated greater feasibility for detecting primary and metastatic prostate cancer, with significantly more lesions detected on ^{18}F-choline PET as compared to conventional ^{18}F-fluorodeoxyglucose (FDG) PET in both castrate and non-castrate prostate cancer. Cimitan et al. reported that in patients who have previously undergone treatment, skeletal or visceral metastases were more likely to be detected by ^{18}F-choline PET/CT if the PSA level was greater than 4.0 ng/ml [19]. In contrast, Heinisch et al. [8] found that ^{18}F-choline PET/CT could consistently yield true positive results at PSA levels of less than 5.0 ng/ml, although this study included mostly patients who have had radical prostatectomy. Feasibility for detecting localized recurrence following radical prostatectomy with PSA levels of less than 1.0 ng/ml was also reported in a study by Vees et al. [20]. In the current study, lesions were more likely to be detected at a PSA of greater than 4.0 ng/ml, although it was still possible to detect smaller non-measurable lesions at PSA levels below 4.0 ng/ml. Unlike these other studies, the current study was not intended to evaluate ^{18}F-choline PET/CT as a staging tool because most patients with metastatic cancer are unlikely to benefit from non-systemic treatment of their disease. Rather, the aim of this study was to assess feasibility for identifying target lesions for monitoring, because the ability to accurately monitor lesions during therapy could ultimately hasten the discovery of new systemic agents for enhancing survival in HRPC.

In this study, the skeletal findings on ^{18}F-choline PET/CT corresponded well to radionuclide bone scan findings. Although RECIST omits skeletal lesions, the ability of ^{18}F-choline PET/CT to localize skeletal lesions raises the possibility of morphometric or metabolic assessment of bone metastases by other criteria. There have already been attempts to adopt RECIST to skeletal lesions imaged by MRI [21]. Because whole-body MRI has not yet become practical, whole-body ^{18}F-choline PET/CT may help to direct MRI toward measurable lesions. An observation in this study that treated bone metastases can have decreasing but persistent activity on serial radionuclide bone scans without significant uptake of ^{18}F-choline raises the possibility that ^{18}F-choline PET/CT is more specific than bone scans for post-treatment monitoring of skeletal disease. Additional studies evaluating ^{18}F-choline PET/CT as a means of gauging skeletal tumor response are needed to further test this possibility.

Conventional PET imaging with ^{18}F-FDG has also been studied as a means of monitoring disease progression in HRPC. While this technique is generally considered to have low sensitivity for prostate cancer [22–24], it may have some value for gauging responses to systemic therapies in advanced prostate cancer [25, 26]. In a study by Morris et al., the appearance of new lesions on ^{18}F-FDG PET, or a 33% or greater increase in the SUV_{max} of an existing lesion, could reliably distinguished progressors from non-progressors after docetaxel-based chemotherapy [26]. It would be of interest to include comparisons with ^{18}F-FDG PET/CT in future evaluations of ^{18}F-choline PET/CT for HRPC.

The limitations of this study are worth noting. Most importantly, the majority of lesions in this study were not biopsied. Without a histologic standard of reference, the diagnostic sensitivity and specificity of ^{18}F-choline PET/CT could not be estimated accurately. Because of the preliminary nature of this study, it was impractical to pursue routine biopsy due to issues of morbidity, sampling error, and the lack of specificity for many conventional imaging results. Although histopathologic confirmation is not mandated by RECIST, the application of ^{18}F-choline PET as a tumor response measure should await further histopathological validation. The results of this study merely support the feasibility of applying RECIST to aid in the evaluation of ^{18}F-choline PET/CT as a response marker. Further studies in a greater number patients with varying PSA levels would be required to accurately evaluate lesion detection at different PSA levels, as well as to determine whether ^{18}F-choline PET/CT can complement PSA for measuring tumor burden and response. Subsequent studies would also benefit by including correlations with clinical outcomes, because better tools for risk-stratification are needed for prostate cancer.

Conclusion

Tumor response measures in clinical trials continue to evolve as molecular imaging techniques gain increasing acceptance in clinical oncology. However, the replacement of morphometric measures with molecular markers as measures of disease progression should proceed cautiously through the validation of molecular imaging techniques by existing criteria and clinical outcome. Comparisons with RECIST appear feasible for evaluations of ^{18}F-choline PET/CT as a therapeutic response marker. The clinical relevance of prostatic and skeletal lesions detected by ^{18}F-PET/CT is also worth investigating, because these potentially significant manifestations of disease are not taken into account by conventional RECIST.

Acknowledgments This work is supported in part by U.S. Army Medical Research and Materiel Command grant W81XWH-05-1-0056 (Prostate Cancer Research Program PC04130) and National Institues of Health/National Cancer Institute grant R41CA110121.

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Protocol Registration Receipt
09/01/2009

Grantor: CDER IND/IDE Number: 66319 Serial Number: 12

Chemotherapy Response Monitoring With 18F-choline PET/CT in Hormone Refractory Prostate Cancer

This study is currently recruiting participants.
Verified by Queen's Medical Centre, September 2009

Sponsored by:	Queen's Medical Centre National Cancer Institute (NCI)
Information provided by:	Queen's Medical Centre
ClinicalTrials.gov Identifier:	NCT00928252

Purpose

The purpose of this study is to determine whether imaging with 18F-choline PET/CT can provide information that may help guide subsequent investigational or clinical treatments for patients with advanced (hormone-refractory) metastatic prostate cancer.

Condition	Intervention	Phase
Hormone Refractory Prostate Cancer	Drug: IV administration of fluorine-18 labeled methylcholine followed by PET/CT	Phase 1/Phase 2

Study Type: Interventional
Study Design: Diagnostic, Single Group Assignment, Open Label, N/A, Efficacy Study
Official Title: Chemotherapy Response Monitoring With 18F-choline PET/CT in Hormone Refractory Prostate Cancer

Further study details as provided by Queen's Medical Centre:

Primary Outcome Measure:

- PSA Outcome [Time Frame: 12 week post-chemotherapy] [Designated as safety issue: No]

Secondary Outcome Measures:

- Brief Pain Inventory [Time Frame: post-chemotherapy] [Designated as safety issue: No]
- Quality of Life (QLQ-30) [Time Frame: post-chemotherapy] [Designated as safety issue: No]

Estimated Enrollment: 25
Study Start Date: June 2009
Estimated Study Completion Date: June 2011
Estimated Primary Completion Date: June 2011

Number of arms: 1
Intervention Details:

Drug: IV administration of fluorine-18 labeled methylcholine followed by PET/CT

Intervention applied at pre-treatment, after 1 cycle, and after 3 cycles of a docetaxel-based chemotherapy regimen.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Male

Inclusion Criteria:

1. Provision of written informed consent.
2. Men, over 18 years of age, with histologically-confirmed diagnosis of prostate cancer
3. History of treatment by complete androgen blockade for greater than 3 months prior to enrollment
4. Serum testosterone level < 50 ng/ml. Castrate testosterone levels must be from orchiectomy or current therapy with luteinizing hormone-releasing hormone agonist.
5. Progressive disease evidenced by 2 consecutive rises in PSA measured at least 1 week apart, with the absolute value of the latest PSA > 5.0 ng/ml.
6. A rise in PSA following anti-androgen drug withdrawal, above the last PSA value before withdrawal.
7. Patient is under the care of a medical oncologist and has agreed to treatment with a docetaxel-based chemotherapy regimen that is consistent with current standards of care.

Exclusion Criteria:

1. Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of basal cell carcinoma or superficial transitional cell carcinoma of the bladder.
2. Serious underlying medical conditions that would otherwise impair the patient's ability to undergo imaging.
3. Patient weighs over 350 lbs (due to scanner weight limit).
4. Clinical life expectancy < 12 weeks.
5. Participated in other radioactive drug studies where estimated total cumulative dose within 1 year is > 0.05 Sievert for whole body, active blood-forming organs, eye lens, gonads, or 0.15 Sievert for other organs.
6. Concurrent Therapy. Allowed: Prior or concurrent chemotherapy, but must be > 12 weeks since last treatment at enrollment; prior or concurrent hormonal therapy; prior surgery; prior or concurrent bisphosphonate; prior or concurrent receptor/biologic agent allowed if given on study protocol (e.g., SWOG

S0421: Addition of atrasentan to docetaxel/prednisone). Not allowed: concurrent radiotherapy or radioisotope therapy (e.g., strontium). Other: Prior radiotherapy or radioisotope therapy must be >12 weeks since last treatment.

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Principal Investigator: Sandi A Kwee, MD

Investigators

Principal Investigator:	Sandi A Kwee, MD	The Queen's Medical Center

More Information

Responsible Party:	The Queen's Medical Center (Sandi Alexander Kwee, MD)
Study ID Numbers:	RA-2008-069, R21CA139687
Health Authority:	United States: Food and Drug Administration

Protocol Registration Receipt
09/01/2009

Grantor: CDER IND/IDE Number: 66319 Serial Number: 12

Measurement of Anti-Androgen Response Using 18F-choline PET/CT in Androgen-Insensitive Prostate Cancer

This study is currently recruiting participants.
Verified by Queen's Medical Centre, September 2009

Sponsored by:	Queen's Medical Centre National Cancer Institute (NCI)
Information provided by:	Queen's Medical Centre
ClinicalTrials.gov Identifier:	NCT00928174

Purpose

The purpose of this study is to determine whether PET/CT using 18F-choline as an imaging agent can characterize regional responses to anti-androgen therapies in a manner that in the future aid in the customized planning of treatments for patients with androgen-insensitive prostate cancer.

Condition	Intervention	Phase
Prostate Cancer	Drug: IV administration of fluorine-18 methylcholine followed by PET/CT imaging	Phase 1/Phase 2

Study Type: Interventional
Study Design: Diagnostic, Single Group Assignment, Open Label, N/A, Safety/Efficacy Study
Official Title: Measurement of Anti-Androgen Response Using 18F-choline PET/CT in Androgen-Insensitive Prostate Cancer

Further study details as provided by Queen's Medical Centre:

Primary Outcome Measure:

- PSA Outcome [Time Frame: 30-75 day follow-up] [Designated as safety issue: No]

Estimated Enrollment: 21
Study Start Date: June 2009
Estimated Study Completion Date: June 2011
Estimated Primary Completion Date: June 2011

Number of arms: 1
Intervention Details:
Drug: IV administration of fluorine-18 methylcholine followed by PET/CT imaging
Imaging intervention performed prior to and 30-75 days post a change in anti-androgen therapy.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Male

Inclusion Criteria:

1. Provision of written informed consent.
2. Men, over 18 years of age, with histologically-confirmed diagnosis of prostate cancer
3. History of treatment by complete androgen blockade for greater than 3 months prior to enrollment
4. Serum testosterone level < 50 ng/ml. Castrate testosterone levels must be from orchiectomy or current therapy with leutinizing hormone-releasing hormone agonist.
5. Progressive disease evidenced by two consecutive rises in PSA above a nadir value, with the absolute value of the latest PSA > 2. 0 ng/ml.
6. Patient will be undergoing a therapeutic intervention under the supervision of his treating physician (urologist, oncologist).

Exclusion Criteria:

1. Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of basal cell carcinoma or superficial transitional cell carcinoma of the bladder.
2. Serious underlying medical conditions that would otherwise impair the patient's ability to undergo imaging.
3. Patient weighs over 350 lbs (due to scanner weight limit).
4. Clinical life expectancy < 12 weeks.
5. Participated in other radioactive drug studies where estimated total cumulative dose within 1 year is > 0.05 Sievert for whole body, active blood-forming organs, eye lens, gonads, or 0.15 Sievert for other organs.
6. Concurrent Therapy. Allowed: prior hormonal therapy; concurrent LHRH agonist; prior surgery; prior or concurrent bisphosphonate. Not allowed: concurrent anti-androgen or secondary hormonal therapy, prior or concurrent chemotherapy, concurrent radiotherapy or radioisotope therapy (e.g., strontium). Other: Prior radiotherapy or radioisotope therapy must be > 12 weeks since last treatment.

Contacts and Locations

Contacts

Karen Ng, RN	808-537-7614	kng@queens.org
Sandi A Kwee, MD	808-585-5466	skwee@queens.org

Locations

United States, Hawaii

The Queen's Medical Center — Recruiting

Honolulu, Hawaii, United States, 96813

Contact: Karen Ng, RN 808-537-7614 kng@queens.org

Contact: Sandi A Kwee, MD 808-585-5466 skwee@queens.org

Principal Investigator: Sandi A Kwee, MD

Investigators

Principal Investigator:	Sandi A Kwee, MD	The Queen's Medical Center

More Information

Responsible Party:	The Queen's Medical Center (Sandi Alexander Kwee, MD)
Study ID Numbers:	RA-2009-009, R21CA139687
Health Authority:	United States: Food and Drug Administration

APPENDIX 4:

Principal Investigator CV

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Sandi Alexander Kwee	Assistant Professor, Univ. Hawaii; Research Director, Hamamatsu/Queen's PET Center.

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Carnegie Mellon University, Pittsburgh, PA	B.S.	1987-1991	Electrical Engineering
University of Pittsburgh, Pittsburgh, PA	M.D.	1992-1996	Medicine
University of Hawaii Residency Program, Honolulu, HI		1996-1999	Internal Medicine
University of Washington, Seattle, WA		2000-2002	Nuclear Medicine/PET

POSITIONS / PROFESSIONAL EXPERIENCE

1988-1991	Computer Programmer, PPG Industries & Department of Economics, Carnegie Mellon University, Pittsburgh, PA
1991-1992	Research Assistant, Neurobehavioral Studies Program, Western Psychiatric Institute and Clinic, Pittsburgh, PA
1996-1999	Internship and Residency, University of Hawaii Internal Medicine Residency Program, Honolulu, HI
1999-2000	Physician, Family Medicine, Internal Medicine, and Urgent Care, Waianae Coast Comprehensive Health Center, Waianae, HI
1999-present	Medical Staff, The Queen's Medical Center, Honolulu, HI
1999-2000	Medical Staff, Saint Francis Medical Center, Ewa Beach, HI
2000-2002	Fellow, Nuclear Medicine and PET, University of Washington, Seattle, WA
2001-2002	Physician, Emergency Department, Department of Veterans Affairs-Puget Sound Health Care System, Seattle, WA
2001-2003	Medical Officer, Seattle Division- Department of Veterans Affairs, Puget Sound Health Care System, Seattle, WA
2002-2004	Research Fellow, The Queen's Medical Center, Honolulu, HI
2003-2005	Member, Brain Imaging Council, Society of Nuclear Medicine, Term 2003-2005.
2004-2005	Research Associate, The Queen's Medical Center, Honolulu, HI
2004-present	Assistant Professor, Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2004-present	Clinical Assistant Professor, Department of Geriatric Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2004-present	Member, Cancer Committee, The Queen's Medical Center, Honolulu, HI
2005-present	Director of Research, Hamamatsu/Queen's PET Imaging Center, Honolulu, HI
2005-present	Member, University of Hawaii, Cooperative Institutional Review Board (IRB)
2005-present	Associate Member, University of Hawaii Cancer Research Center Clinical Sciences Program

CERTIFICATION

1999	American Board of Internal Medicine
2002	American Board of Nuclear Medicine
2004	Certification Board of Nuclear Cardiology

HONORS AND AWARDS

Research Scholarship in Neuropsychiatry, University of Pittsburgh Medical Center, 1991

Medical Student Research Excellence Award, University of Pittsburgh School of Medicine, 1993.

Scientific Award, Annual Straehley Symposium, Kaiser Foundation, November 1997.

Invited Reader, Japan-US Joint Film Reading Conference. 41st Annual Meeting of the Japanese Society of Nuclear Medicine, October 2001.

Asa Seeds Award (Radiology, Dept. Division of Nuclear Medicine), University of Washington, 2002

SELECTED PUBLICATIONS

Kwee SA. Coel MN. Lim J. Ko JP. Combined Use of F-18 Fluorocholine PET and Magnetic Resonance Spectroscopy for Brain Tumor Evaluation. Journal of Neuroimaging. 2004 July. 14(3): 285-289.

Kwee SA, Coel MN, Lim J, Ko JP. Sextant Localization of Prostate Cancer with F-18 Fluorocholine Positron Emission Tomography. J Nucl Med May 2004. 45(5 Suppl) : 397

Liu K. **Kwee SA.** Demographic, Treatment, and Survival Patterns for Native Hawaiians with Lung Cancer Treated at a University Affiliated Medical Center from 1995 to 2001. Pacific Health Dialog. 2004 September. 11(2): 139-145.

Harbert MI, **Kwee S,** Picket-Gies CA. Sodium iodide symporter expression in iodine-refractory thyroid cancer. Journal of Investigative Medicine. Feb 2003; 51: S117-118

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Kwee SA, Wei H, Yun D, Sesterhenn I, Coel MN. Localization of Primary Prostate Cancer with Dual-phase 18F-Fluorocholine PET. Journal of Nuclear Medicine. 2006 Feb; 47: 262-269.

Kwee SA, Ko JP, Jiang CS, Watters M, Coel MN. Evaluation of MRI Enhancing Solitary Brain Lesions Using Fluorine-18 Fluorocholine Positron Emission Tomography. Solitary Brain Lesions Enhancing at MR Imaging: Evaluation with Fluorine 18-Fluorocholine PET. Radiology. 2007 Jun 20; PMID: 17581887

Kwee SA, DeGrado TR, Talbot JN, Gutman F, Coel MN. Cancer Imaging with Fluorine-18 Labeled Choline Derivatives. Seminars in Nuclear Medicine. 37: 420-428. November 2007.

DeGrado T, **Kwee SA,** Coel MN, Coleman RE. The Impact of Urinary Excretion of ^{18}F-Labeled Choline Analogs J Nucl Med 2007 48: 1225 (letter)

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Use of Step-Section Histopathology to Evaluate 18F-Fluorocholine PET Sextant Localization of Prostate Cancer. Molecular Imaging 2008. Jan-Feb;7(1): 12-20.

Kwee SA, Degrado T. Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels. Eur J Nucl Med Mol Imaging. 2008 Aug; 35(8): 1567-9.

Kwee SA, Coel MN, Ly BH.18F-choline PET/CT Imaging of RECIST Measurable Lesions in Androgen Insensitive Prostate Cancer. Annals of Nuclear Medicine. 2009 Aug; 23(6): 541-548

Kwee SA, Coel MN. Detection of Synchronous Primary Breast and Prostate Cancer by F-18 fluorocholine PET/CT. Clinical Nuclear Medicine. 2010 Feb; 35(2): 100-102

SCIENTIFIC ABSTRACTS (ORAL PRESENTATIONS)

Kwee S, Ko JP, Coel M. *Use of F-18 Fluorocholine PET and Magnetic Resonance Spectroscopy for Brain Tumor Evaluation.* The 10th Conference of Peace through Mind Brain Science. February 25 – February 27, 2004, Hamamatsu City, Japan.

Kwee S, Lim J, Ko JP, Coel M. *Sextant Localization of Prostate Cancer with F-18 Fluorocholine Positron Emission Tomography.* Scientific Paper Presentation: Prostate Cancer. 51st Annual Meeting. Society of Nuclear Medicine. Philadelphia PA. 2004.

Kwee S. *Fluorine-18 Labeled Choline Derivatives for Brain Tumor PET Imaging.* The Eleventh Conference of Peach through Mind-Brain Science. Research Foundation for Opto-Science and Technology. Ministry of Education, Culture, Sports, Science and Technology, Japan. Shizuoka Prefecture. February 20-22, 2006.

Kwee S, Ko JP, Jiang CS, Watters M, Lim J, Coel MN. *Differentiation Between High-Grade Gliomas and Solitary Brain Metastases: Tumoral and Peritumoral Assessment with Fluorine-18 Fluorocholine Positron Emission Tomography.* Society of Molecular Imaging Annual Meeting, August 2006.

G. Thibault, R. Stack, **S. A. Kwee**, B. Furusato, M. Coel and I. Sesterhenn. *Initial Results From a Whole Prostate Histopathologic Correlation Study.*, American Urologic Association – Western Section. Annual Meeting. October 2006.

Yun DY, **Kwee SA**, Wei H, Coel M. *A Surface Adaptive Region Growing Algorithm for Tumor Localization, Object Reconstruction and Shape Visualization*. IEEE 2006 Nuclear Science Symposium and Medical Imaging Conference. October 2006.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Non-Invasive Detection and Therapeutic Targeting of Cancer in the Prostate Using Fluorine-18 Fluorocholine Positron Emission Tomography. IMPact 2007, Atlanta, GA.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Prostate Imaging with 18F-Fluorocholine Using a Whole-Body Positron Emission Tomograph. Nuclear Science Symposium / Medical Imaging Conference Institute of Electrical and Electronics Engineers 2007.

Park H, **Kwee S**, Thibault G, Stack G, Furusato B, Sesterhenn I, Meyer CR. Registration Methods for Histological Slides and *ex vivo* MRI of Prostate. Nuclear Science Symposium / Medical Imaging Conference Institute of Electrical and Electronics Engineers 2007.

Kwee SA, Coel MN, Lim J. Longitudinal 18F-choline PET/CT imaging in prostate cancer patients with increased risk of disease progression. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Narayanan M, **Kwee SA**, Coel MN, Lim J. Kinetic analysis of 18F-choline PET/CT images for sextant localization of primary prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Kwee SA, Ly B, Coel MN. RECIST measurability of 18F-choline PET/CT detected lesions in androgen insensitive prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

OTHER SCIENTIFIC ABSTRACTS (POSTERS)

Kohli V, **Kwee SA**, Coel MN. *Comparison between 2D and 3D Prostate PET Imaging.* J. Nucl. Med., May 2006; 47: 370P.

Kwee SA, Turner H, Lim J, Wakano C, Coel M. *Dimethylaminoethanol Reduces 18F-Fluoroethylcholine Uptake in Prostate Cancer Cells.* J. Nucl. Med., May 2006; 47: 425P.

Kwee S, Wei H, Sesterhenn IA, Yun DY, Coel MN. *Intensity Modulated Radiation Therapy For Prostate Cancer With Radiation Dose Augmentation Guided By 18F-FCH PET Imaging.* J. Nucl. Med., May 2006; 47: 457P.

Kwee SA, Thibault G, Stack R, Furusato B, Coel M, Sesterhenn IA. *Cancer Localization in the Prostate with 18F-Fluorocholine PET: Initial Results From a Whole Prostate Histopathologic Correlation Study.* J. Nucl. Med., May 2006; 47: 459P.

Lim J, **Kwee S**, Cabral C, Turner H, Wakano C, Stokes A, Coel M. *Automated Synthesis and In Vitro Uptake of [18F] Fluoroethylcholine in Prostate Cancer*. Molecular Imaging July-September 2006 5(3).

Kwee S, Ko JP, Jiang CS, Watters M, Lim J, Coel MN. *Fluorine-18 fluorocholine PET Evaluation of Brain Tumor Recurrence Following Radiation Therapy.* Proceedings of the 9th World Congress of Nuclear Medicine and Biology. Seoul, Korea. October 2006.

FEDERAL AGENCY RESEARCH SUPPORT

Positron Emission Tomography Guided Prostate Biopsy
R41CA110121 9/2004 – 3/2006
National Institutes of Health, National Cancer Institute
Role:Co-Investigator

Cancer Localization in the Prostate with 18F-Fluorocholine Positron Emission Tomography
Congressionally Directed Medical Research Programs, New Investigator Award
PC040130
Dates: 7/2004 – 7/2009
Role: Principal Investigator

Treatment Effects on Tumor 18F-Choline Metabolism in Advanced Prostate Cancer
National Institutes of Health, National Cancer Institute
R21CA139687
Dates: 7/2009 – 6/2011
Role: Principal Investigator